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EXPERIMENTAL STUDIES

Influence of Infarct Age on Reproducibility of Ventricular Tachycardia Induction in a Canine Model

GERALDINE B. HUNT, BVSc, DAVID L. ROSS, MBBS, FRACP, FACC

Westmead, New South Wales, Australia

The inducibility and reproducibility of ventricular tachycardia were evaluated in 97 dogs after myocardial infarction produced by single stage coronary artery ligation. Arrhythmia induction was performed with use of an endocardial electrode catheter positioned at the right ventricular apex before each study. An aggressive protocol of programmed stimulation was used, employing up to seven extrastimuli and three attempts at arrhythmia induction in each study. Electrophysiologic study was performed in individual dogs at the following times after infarction: 1) 7.7 ± 0.3 and 15 ± 0.2 days (34 consecutive dogs); 2) 14 ± 0.6 and 26 ± 1.7 days (24 selected dogs); 3) 19 ± 2 and 43 ± 3 days (12 selected dogs); 4) 36 ± 2 and 60 ± 6 days (8 selected dogs); and 5) 59 ± 12 and 130 ± 10 days (3 selected dogs).

Inducibility of ventricular tachycardia decreased significantly from 74% 1 week after infarction to 41% 2 weeks after infarction. Thus, early reproducibility was low (48%). Reproducibility increased thereafter, with 88% of the dogs having reproducible ventricular tachycardia between 2 and 4 weeks ($p < 0.025$) and 100% having reproducibly inducible ventricular tachycardia between 4 weeks and 4 months after infarction. Dogs with no inducible arrhythmia early after infarction did not develop inducible ventricular tachycardia or fibrillation at later studies.

Twelve dogs developed spontaneous ventricular tachycardia or sudden arrhythmic death late after infarction. Overall, 22% of dogs with inducible ventricular tachycardia with a cycle length >140 ms developed spontaneous ventricular tachycardia or sudden death.

Arrhythmia induction decreases significantly during the 1st 2 weeks after myocardial infarction, but long-term reproducibility of ventricular tachycardia induced ≥2 weeks after infarction is very high. This canine model of long-term, reliably inducible ventricular tachycardia is suitable for investigation of antiarrhythmic drugs, surgery and other interventions.

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Electrophysiologic study is used to determine patient predisposition to the occurrence of life-threatening ventricular tachyarrhythmias in the 1st year after myocardial infarction (1–4). However, in some patients early ventricular tachycardia induction is not reproducible over long periods of time, and inducibility decreases as the infarct ages (3,4). Marked electrophysiologic and anatomic changes have been documented (5,6) during the healing and maturation of experimental canine infarction, and it is likely that the arrhythmia substrate is modified by this process. It is therefore important to determine when changes in the inducibility of ventricular tachycardia occur after infarction, thereby avoiding unnecessary long-term antiarrhythmic interventions.

Previous canine studies have yielded conflicting results. Garan et al. (7) observed minimal change in the inducibility of ventricular tachycardia between 1 and 6 weeks after single stage permanent coronary occlusion. In contrast, Duff et al. (8) identified a subgroup of dogs in which inducibility of ventricular tachyarrhythmias was lost during the first 4 weeks after infarction produced by the occlusion-reperfusion technique. No study has yet evaluated the stability of the induction of ventricular tachycardia over a longer period (>6 weeks) or the potential for spontaneous arrhythmic events in dogs late after infarction.

The aim of the present study was to determine when ventricular tachycardia became reproducible after infarction and whether it remained inducible during infarct maturation in a canine model of single stage coronary occlusion. Electrophysiologic variables were evaluated in an attempt to identify the subgroup of dogs in which arrhythmia induction was likely to be lost. Finally, spontaneous ventricular ar-

From the Cardiology Unit, Department of Medicine, Westmead Hospital, Westmead, New South Wales, Australia. This project was funded by a grant from the National Health and Medical Research Council of Australia, Canberra, Australian Capital Territory, Australia.

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Address for reprints: David L. Ross, Cardiology Unit, Department of Medicine, Westmead Hospital, Westmead, New South Wales 2145, Australia.

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rhythmias were documented and compared with the results of previous electrophysiologic study in individual dogs.

Methods

This project was approved by the Westmead Hospital Research and Animal Care Committees. It conforms to the position of the American Heart Association on research animal use.

Animal preparation. Anesthesia was induced in mongrel dogs weighing between 15 and 35 kg with use of intravenous thiopental (20 mg/kg body weight). Dogs were then intubated and artificially ventilated with a Harvard respirator (15 ml/kg; 15 breaths/min). Anesthesia was maintained with halothane (1% to 2%) delivered by an out of circuit precision vaporizer (Fluotec Mk III Cyprane, Keighley) in a 1:2 oxygen to nitrous oxide mixture.

With use of sterile technique, a thoracotomy was performed in the left fourth or fifth intercostal space (over the palpable cardiac impulse), and the heart was suspended in a pericardial cradle. Lidocaine (2 mg/kg) was administered intravenously. The left anterior descending coronary artery was ligated both at the tip of the left atrial appendage and 2 to 3 cm distally. The first two diagonal branches between these points were also ligated.

The thoracotomy was then closed, and the dogs allowed to recover. Bupivicaine (a long-acting local anesthetic agent) was infiltrated around the third to fifth or fourth to sixth left intercostal nerves to provide postoperative analgesia. Prophylactic quinidine hydrochloride (a long-acting preparation) was administered orally (200 to 400 mg twice daily) for 48 h after operation to the majority of dogs.

Results from 97 surviving dogs make up the basis of this report. An additional 20 dogs with inducible ventricular tachycardia, forming part of another experimental series, were also observed for the occurrence of spontaneous ventricular arrhythmias.

Electrophysiologic Study

Anesthesia for electrophysiologic study. Electrophysiologic study was performed in both conscious and anesthetized dogs. The same experimental protocol was used each time an individual dog was studied to reduce study to study variation (for example, Dog 1 always underwent conscious electrophysiologic study, whereas Dog 2 always underwent electrophysiologic study while anesthetized with one particular anesthetic agent or combination of agents). The following anesthetic regimens were used for electrophysiologic study: 1) pentobarbitone (30 mg/kg intravenously) was used in the first 20% of dogs because it is a standard agent for experimental canine anesthesia; 2) fentanyl (38 μg/kg) and droperidol (1.8 mg/kg intramuscularly) followed by inhalation of a 1:3 mixture of oxygen and nitrous oxide, a combination which we have shown (9) to have minimal influence on arrhythmia induction; or 3) droperidol (1 mg/kg intravenously) followed by ketamine (10 mg/kg intravenously).

Preparation of electrodes for electrophysiologic study. Dogs intended for conscious electrophysiologic study were anesthetized 24 h before study with thiopental and halothane in a nitrous oxide mixture. A quadripolar electrode catheter was positioned at the right ventricular apex after sterile exposure of an external jugular vein. The catheter plugs were secured at the nape of the neck, and the dogs allowed to recover. The electrode catheters were removed after each day of study and reimplanted for electrophysiologic study on subsequent days.

In the remaining dogs, anesthesia was induced with one of the anesthetic regimens just described, and a quadripolar electrode catheter was positioned at the right ventricular apex by means of percutaneous puncture of an external jugular vein immediately before electrophysiologic study.

Electrophysiologic protocol. One to three surface Frank vectorcardiographic leads (X, Y and Z, similar to electrocardiographic [ECG] leads I, aVF and V_1) were recorded simultaneously with an intracardiac ventricular electrogram using an ink-jet recorder (Mingograf, Siemens-Elema) at speeds of 25 to 100 mm/s. The protocol for programmed stimulation consisted of right ventricular apical stimulation at twice diastolic threshold (pulse width 2 ms) with use of a battery-powered stimulator (WPI model 520, World Precision Instruments). A drive train of eight paced beats was delivered at a cycle length 50 ms shorter than the spontaneous sinus cycle length. This was followed by an extrastimulus delivered during mid-diastole, commencing with a coupling interval of 200 ms. The coupling interval of this extrastimulus was reduced in 10 ms decrements until ventricular refractoriness was encountered. The coupling interval was then set 10 ms outside the refractory period, and further extrastimuli were added in the same manner until a ventricular arrhythmia lasting >10 s was induced or the maximum of five to seven extrastimuli were delivered. Ventricular tachycardia was considered to be sustained if it lasted ≥10 s; almost invariably, monomorphic tachycardia lasting ≥10 s required overdrive pacing or direct current shock for termination. Arrhythmia induction was attempted at least two and usually three times during 1 day. The interval between studies was 2 h in conscious dogs and 10 to 15 min in anesthetized dogs.

Determination of Arrhythmia Reproducibility

Reproducibility between 1 and 2 weeks after infarction. Thirty-four consecutive dogs (26 anesthetized, 8 conscious) underwent electrophysiologic study at both 7.7 ± 0.3 and 15 ± 0.2 days after infarction. The results of the 15 day study in these dogs were also compared with those of another group

of 50 dogs that underwent their first electrophysiologic study 14.5 ± 0.3 days after infarction.

Reproducibility between 2 and 4 weeks after infarction. Twenty-three dogs from the two groups just described underwent electrophysiologic study at both 14 ± 0.6 and 26 ± 1.7 days after infarction (10 anesthetized, 13 conscious).

Reproducibility between 3 and 6 weeks after infarction. Twelve dogs underwent electrophysiologic study while conscious at both 19 ± 2 and 43 ± 3 days after infarction.

Reproducibility between 5 and 8 weeks after infarction. Eight dogs underwent electrophysiologic study while conscious 36 ± 2 and 60 ± 6 days after infarction.

Reproducibility between 8 weeks and 4 months after infarction. Three dogs underwent further electrophysiologic study while conscious 2 months (59 ± 12 days) and again at ≥4 months after infarction (130 ± 10 days).

Frequency of study. The groups just described are not mutually exclusive. A total of 10 dogs with inducible ventricular tachycardia underwent electrophysiologic study on ≥3 occasions between 18 ± 1.5 and 72 ± 12 days after infarction. Because many dogs with inducible ventricular tachycardia entered another experiment 4 weeks after infarction and because it was not possible to keep dogs without inducible tachyarrhythmia for long periods of time, all dogs do not appear in every group. Dogs without inducible arrhythmia are not well represented in later groups. Most dogs (63%) only appear in one group, 35% appear in two groups and only one dog appears in three groups. In all dogs with reproducible ventricular tachycardia, changes in tachycardia cycle length and configuration between studies were analyzed.

Animal monitoring. Dogs were observed daily and received a clinical examination and ECG if any signs of illness were noticed. The most common signs demonstrated by dogs in which sustained spontaneous ventricular tachycardia was documented were lethargy, anorexia and hyperpnea or dyspnea. Seven lead ECG (six aVF leads and lead V_1) or three lead Frank vectorcardiographic (leads X, Y and Z) recordings were taken in all dogs during spontaneous ventricular tachycardia. An arrhythmic event was presumed to be the cause of death in four dogs seen to be well 10 min to 12 h before being found dead. Postmortem examination of these dogs excluded any other life-threatening disease.

Statistical analysis. Electrophysiologic variables were compared among studies by Student's *t* test for paired continuous data and among groups by Student's unpaired *t* test. McNemar's test of correlated proportions was used to compare the results of different electrophysiologic studies in the same dogs. Chi-square analysis was used to compare independent proportions. Probability (p) values <0.05 were considered significant. All values are expressed as mean values ± SEM.

Table 1. Electrophysiologic Data from 34 Group 1 Dogs 1 and 2 Weeks After Infarction and 50 Group 2 Dogs 2 Weeks After Infarction

	Group 1		Group 2
Days after infarction	7.7 ± 0.3	15 ± 0.2	14.5 ± 0.3
Heart rate (beats/min)	140 ± 6	144 ± 5	138 ± 5
Drive train cycle length (ms)	345 ± 7	337 ± 6	353 ± 6
Ventricular refractory period (ms)	136 ± 3	136 ± 2	137 ± 2
Inducible VT (%)	74	41*	50
VT cycle length (ms)	146 ± 7	146 ± 9	152 ± 8
Extrastimuli (VT)	3.1 ± 0.2	3.5 ± 0.3	3.4 ± 0.1
Inducible VF (%)	20	21	14
Extrastimuli (VF)	2.8 ± 0.2	3.9 ± 0.4	3.9 ± 0.3
No inducible arrhythmia (%)	6	38*	36

*15 day value significantly different from 7 day value. All data are expressed as mean ± standard error of the mean. Extrastimuli = number of extrastimuli required for induction of ventricular arrhythmia; VF = ventricular fibrillation; VT = ventricular tachycardia.

Results

Inducibility and Reproducibility of Arrhythmia Induction During Infarct Healing and Maturation

Reproducibility between 1 and 2 weeks after infarction (Group 1) (Table 1). Thirty-four dogs underwent electrophysiologic study 7.7 ± 0.3 days after infarction. No dog demonstrated any spontaneous ventricular tachycardia at >2 days after infarction. All dogs were in sinus rhythm at the time of electrophysiologic study, and arrhythmia induction was attempted at least twice in each dog during 1 day. Eighty percent of dogs had three inductions during 1 day.

Eight days after infarction 25 (74%) of the 34 dogs had sustained ventricular tachycardia induced. In all cases, this ventricular tachycardia could be reinduced at least once more during the same day. Seven dogs (20%) had ventricular fibrillation induced and two dogs (6%) had no inducible arrhythmia despite the use of at least five extrastimuli.

The same 34 dogs underwent electrophysiologic study again 15 ± 0.2 days after infarction under similar experimental conditions (Table 1). Thirteen (52%) of the 25 dogs with ventricular tachycardia at 7 days no longer demonstrated inducible sustained ventricular tachycardia. Two dogs that had ventricular fibrillation at 7 days demonstrated ventricular tachycardia at the study on day 15. Therefore, 2 weeks after infarction, only 14 (41%) of 34 dogs had inducible ventricular tachycardia. The cycle length of ventricular tachycardia was not significantly different from that induced in the same dogs at 7 days (145 ± 9 ms, $p = 0.21$) and its induction required a similar number of extrastimuli (3.0 ± 0.2, $p = 0.25$). Reproducibility of the induction of ventricular tachycardia between 7 and 15 days was only 48% ($p < 0.01$)

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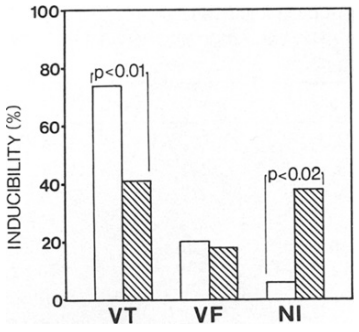

Figure 1. Change in inducibility of ventricular arrhythmias between 7 and 15 days after myocardial infarction in 34 dogs. Note that the proportion of dogs with no inducible arrhythmia increases significantly between 7 and 15 days at the expense of ventricular tachycardia (VT) induction. NI = no inducible arrhythmia; VF = ventricular fibrillation. **Open bars** = 7 days; **hatched bars** = 15 days postinfarction.

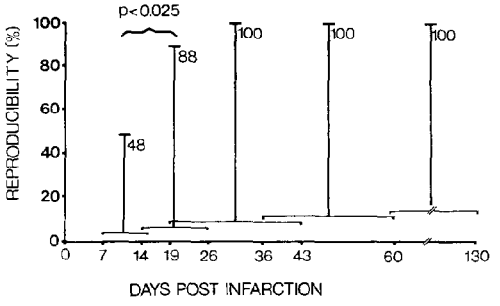

Figure 2. Histograms depicting the reproducibility of ventricular tachycardia induction at varying intervals after myocardial infarction; 7 to 15 days (n = 34), 14 to 26 days (n = 23), 19 to 43 days (n = 12), 36 to 60 days (n = 8) and 59 to 130 days (n = 3). The percent of dogs in which ventricular tachycardia was inducible during each of these intervals is shown beside each histogram. Note that reproducibility of ventricular tachycardia induction increases significantly ($p < 0.025$) from 48% between 7 and 15 days to 88% between 14 and 26 days. Thereafter, reproducibility of induction is 100%.

(Fig. 1). Three (43%) of the 7 dogs studied while conscious and 10 (55%) of the 18 dogs studied under general anesthesia lost ventricular tachycardia inducibility over the same period ($p > 0.1$).

Neither ventricular tachycardia cycle length nor ease of inducibility at 7 days was predictive of the inducibility of ventricular tachycardia 1 week later. When results from the 7 day study were compared, the subgroup of dogs in which the arrhythmia remained inducible at 15 days had ventricular tachycardia with a cycle length of 145 ± 9 ms induced with 3 ± 0.4 extrastimuli. The subgroup of dogs in which the inducibility of ventricular tachycardia was lost had ventricular tachycardia with a cycle length of 147 ± 9 ms ($p = 0.45$) induced with 3.2 ± 0.2 extrastimuli ($p = 0.22$). The incidence of inducible ventricular fibrillation at 2 weeks was 21% ($p < 0.02$) and that of no inducible arrhythmia was 38%.

An additional group of 50 dogs (Group 2) that underwent their first *electrophysiologic study 10 to 16 days (mean 14.5 ± 0.3) after infarction were also studied (Table 1).* Twenty-five dogs (50%) had sustained ventricular tachycardia induced. The cycle length of ventricular tachycardia and number of extrastimuli required were not significantly different from values recorded for Group 1 dogs 15 days after infarction ($p = 0.3$ and 0.27, respectively). Seven (14%) of the 50 dogs had ventricular fibrillation induced, and 18 (36%) had no inducible arrhythmia. These values are not significantly different from those observed for dogs in Group 1 (Table 1).

Reproducibility between 2 and 4 weeks after infarction. Twenty-three dogs (11 in Group 1, 12 in Group 2) that had been studied 2 weeks (14 ± 0.6 days) after infarction also underwent electrophysiologic study approximately 4 weeks (26 ± 1.7 days) after infarction. Ten dogs from Group 1 were anesthetized, and the remaining 13 were studied while conscious.

Fourteen days after infarction, 16 of the 23 dogs had ventricular tachycardia of cycle length 148 ± 11 ms induced with 3.2 ± 0.3 extrastimuli. Four dogs had ventricular fibrillation induced with 4 ± 0.6 extrastimuli, and 3 dogs had no inducible arrhythmia.

Twenty-six days after infarction, 14 (88%) of the 16 dogs with ventricular tachycardia at 14 days maintained inducibility of ventricular tachycardia at a cycle length of 133 ± 6 ms ($p = 0.1$) with 3.4 ± 0.5 extrastimuli ($p = 0.4$). The increase in reproducibility of ventricular tachycardia from 48% between 7 and 15 days to 88% between 14 and 26 days is significant ($p < 0.025$) (Fig. 2). In addition, one dog with ventricular fibrillation at 14 days had ventricular tachycardia induced 4 weeks after infarction. Interestingly, in both dogs that lost the inducibility of ventricular tachycardia between 14 and 26 days, ventricular tachycardia induced at 2 weeks usually terminated spontaneously between 10 and 20 s. Furthermore, these were the only two dogs in which ventricular tachycardia terminated spontaneously after 10 s. One of these dogs was studied while under anesthesia, the other while conscious. All other dogs required burst pacing or direct current shock to terminate their arrhythmia.

Of the remaining 8 dogs, ventricular fibrillation was induced in 5 (22% of the whole group) with 3.7 ± 0.3 extrastimuli. The reproducibility of ventricular fibrillation induction between 2 and 4 weeks after infarction was 100%. The three dogs with no inducible arrhythmia at 14 days continued to have no inducible arrhythmia.

Reproducibility between 3 and 6 weeks after infarction. Twelve selected dogs underwent electrophysiologic study while conscious 19 ± 2 and again 43 ± 3 days after infarction.

Nineteen days after infarction, 11 of the 12 dogs had ventricular tachycardia (cycle length 151 ± 10 ms) induced with 3.6 ± 0.3 extrastimuli. The remaining dog had ventricular fibrillation induced with three extrastimuli.

Forty-three days after infarction, all 11 dogs maintained ventricular tachycardia with a similar cycle length and number of extrastimuli to that observed at 4 weeks (158 ± 14 ms, 3.5 ± 0.3 extrastimuli; p = 0.17 and 0.43, respectively). Reproducibility of the induction of ventricular tachycardia during this period was 100%. The remaining dog continued to have ventricular fibrillation induced with five extrastimuli.

Reproducibility between 5 and 8 weeks after infarction. Eight dogs underwent electrophysiologic study while conscious at both 36 ± 2 and 60 ± 6 days after infarction.

Five weeks after infarction, six of the eight dogs had ventricular tachycardia (cycle length 128 ± 12 ms) induced with 3.8 ± 0.7 extrastimuli. One dog had ventricular fibrillation induced with five extrastimuli. The remaining dog had no inducible arrhythmia.

Sixty days after infarction, all six dogs maintained inducible ventricular tachycardia with no significant difference in cycle length or number of extrastimuli required (148 ± 16 ms; 3.2 ± 0.7 extrastimuli; p = 0.13 and 0.35, respectively). Therefore, reproducibility of the induction of ventricular tachycardia remained at 100% (Fig. 2). The two remaining dogs had no inducible arrhythmia.

Reproducibility between 2 and 4 months after infarction. Three dogs with inducible ventricular tachycardia underwent electrophysiologic study at both 59 ± 12 and 130 ± 10 days after infarction. In all three dogs, ventricular tachycardia remained inducible during this period, with no significant change in cycle length (133 ± 17 versus 138 ± 10 ms) or number of extrastimuli required (3 ± 0.6 versus 3.6 ± 0.33).

Outcome of multiple electrophysiologic studies. Ten dogs with inducible ventricular tachycardia underwent at least three electrophysiologic studies while conscious between 18 ± 1.5 and 72 ± 12 days after infarction. Electrophysiologic data for these dogs for the first and last study are shown in Table 2. All these dogs had ventricular tachycardia induced at each study and, therefore, reproducibility was 100% between 2 and 10 weeks.

Changes in the configuration of ventricular tachycardia over two or more studies. Ventricular tachycardia induced in the same dogs on different days was not morphologically identical. Alterations in cycle length from 3 to 100% were observed in 87% of dogs. However, cycle length did not change significantly with increasing infarct maturity (Table 2). Ventricular tachycardia induced at the initial study was differentiated into that with a left (84%) or right (16%) bundle branch block configuration. Only 10% of dogs with a left bundle branch block pattern subsequently had right bundle branch block ventricular tachycardia. In contrast, all dogs with a right bundle branch block pattern subsequently had left bundle branch block ventricular tachycardia.

Table 2. Electrophysiologic Data for 10 Dogs With Inducible Ventricular Tachycardia That Underwent Programmed Stimulation on at Least Three Occasions Between 18 ± 1.5 and 70 ± 12 Days After Infarction (first and last studies, respectively)

	Group 1	Group 2	p Value
Days after infarction	18 ± 1.5	72 ± 12	
Heart rate (beats/min)	133 ± 11	128 ± 10	0.38
Drive train cycle length (ms)	374 ± 8	378 ± 8	0.37
Ventricular refractory period (ms)	137 ± 5	143 ± 5	0.33
VT cycle length (ms)	143 ± 10	150 ± 10	0.28
Extrastimuli (VT)	3.6 ± 0.4	3.1 ± 0.4	0.24

All values are expressed as means ± standard error of the mean. Abbreviations as in Table 1.

Spontaneous Arrhythmic Events Late After Myocardial Infarction

Spontaneous ventricular tachycardia. During the course of the present study, eight dogs developed spontaneous documented ventricular tachycardia at least 7 days after infarction (Table 3). Ventricular tachycardia of similar configuration and cycle length to the spontaneous tachycardia in at least two ECG leads was induced at electrophysiologic study in six of seven dogs (spontaneous ventricular tachycardia cycle length 190 ± 10 versus 173 ± 12 ms; p = 0.16) with 3.3 ± 0.3 extrastimuli (Fig. 3). Another dog had nonsustained ventricular tachycardia induced, which lasted for up to 4 s (33 beats), and in the remaining dog spontaneous tachycardia was incessant, preventing electrophysiologic study.

Mortality. Four dogs died suddenly >2 weeks after infarction. Death was witnessed to occur after 5 to 10 min of collapse in one dog with ventricular tachycardia inducible at electrophysiologic study (cycle length 150 ms, three extrastimuli). The remaining three dogs appeared normal at the last observation (a maximum of 12 h before they were found dead). One of these dogs also had ventricular tachycardia induced at electrophysiologic study (Table 3) and another had ventricular fibrillation induced. The remaining dog had not undergone electrophysiologic study before death. Postmortem examination revealed no concurrent life-threatening disease in any of these dogs.

Role of cycle length in subsequent spontaneous ventricular tachycardia and death. The eight dogs with inducible ventricular tachycardia who subsequently had a spontaneous event made up 13% of all dogs with inducible ventricular tachycardia at least 2 weeks after infarction. Interestingly, all eight dogs had ventricular tachycardia with a cycle length of at least 140 ms (range 169 ± 8) induced at electrophysiologic study. This tended to be higher than the ventricular tachycardia cycle length observed for the entire group of dogs with inducible tachycardia. Of all dogs demonstrating inducible ventricular tachycardia with a cycle length >140

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Table 3. Spontaneous Arrhythmic Events and Results of Programmed Stimulation Late After Myocardial Infarction in 12 Dogs

	Spontaneous Arrhythmia			Programmed Stimulation		
Dog No.	Days After Infarction	Event	Cycle Length (ms)	Rhythm	Cycle Length (ms)	EX (VT)
1	7	VT	180	VT	160	4
2	14	VT	220	VT	220	3
3	33 to 50*	VT	170	VT	165	4
4	14 to 21*	VT	220	Incessant VT	Not tested	
5	47	VT	200	VT	140/210	3/4
6	28	VT	150	VT	145	2
7	11	VT	220	VT	140/210	3
8	16	PmVT	160/250	NSVT	120	5
9	20	Witnessed sudden death		VT	150	3
10	15	Sudden death		VT	160	3
11	16	Sudden death		VF		4
12	41	Sudden death		Not tested		

*Multiple events or incessant ventricular tachycardia. EX (VT) = number of extrastimuli required for induction of ventricular tachycardia; NSVT = nonsustained ventricular tachycardia; PmVT = polymorphic ventricular tachycardia; other abbreviations as in Table 1.

ms at least 2 weeks after infarction, 22% developed spontaneous ventricular tachycardia or sudden death.

Discussion

Early loss of ventricular tachycardia inducibility. This study shows that the inducibility of ventricular arrhythmia changes markedly in individual dogs during the early stages of infarct healing. The time course of this decrease in inducibility corresponds to that previously shown (5,6) for electrophysiologic and anatomic alterations after myocardial infarction. Three to 5 days after infarction, surviving myocardial fibers in the ischemic region demonstrated a reduction in membrane potential at rest, action potential amplitude and rate of rise of phase 0 (V max). However, it is reported (5) that 15 days after infarction, most electrophysiologic properties have returned to normal. Resolution of many ultrastructural abnormalities also will have occurred during the same time (6).

Previous canine studies. Previous investigators (10–12) reported changes in arrhythmia inducibility during the 1st week after experimental canine myocardial infarction. However, those studies employed only small numbers of extrastimuli in their stimulation protocol, and changes in arrhythmia inducibility may have been due to spontaneous variability, rather than changes in arrhythmia substrate. In the present study, a standardized protocol employing at least five extrastimuli was used, and multiple inductions were attempted to reduce the influence of baseline variability. Studies in human patients (13,14) have shown that the use of up to five extrastimuli is sufficient to allow for day to day variability in the induction of ventricular tachycardia. Furthermore, in the majority of dogs, electrode catheters were put in place immediately before each study at the standard clinical pacing site (right ventricular apex), a protocol that has been shown to increase the reproducibility of arrhythmia induction in human patients (15).

Garan et al. (7) examined arrhythmia induction in a canine model created by single stage ligation of all coronary arteries supplying the left ventricular apex, and found no significant alteration in the inducibility of ventricular tachycardia between 1 and 6 weeks after infarction. In contrast, Duff et al. (8), using an occlusion/reperfusion model, demonstrated a significant reduction in the inducibility of ventricular tachycardia and fibrillation between 4 days and 4 weeks after infarction, similar to the findings of our study. This discrepancy may reflect the use of different models of myocardial infarction. In the model used by Garan et al. (7), all coronary branches supplying the left ventricular apex were ligated, thus limiting the potential for establishment of collateral circulation to the ischemic area. Infarction produced in this manner was transmural with "a sharply defined border." If restoration of perfusion to the infarct border is prevented, it is likely that most tissue in the ischemic area will die, and marginally ischemic zones will not be salvaged. Therefore, there may be less "remodeling" of the arrhythmia substrate in the first weeks after infarction. In the model used by Duff et al. (8), however, reperfusion of the ischemic area produced a patchy infarct with more potential for resolution of ischemic damage and abolition of arrhythmia substrate by the healing process.

The model used in the present experiment utilizes single stage permanent occlusion, but only of vessels supplied by the left anterior descending coronary artery. Collateral circulation to the ischemic area is still available through the circumflex system. These infarcts are usually transmural at

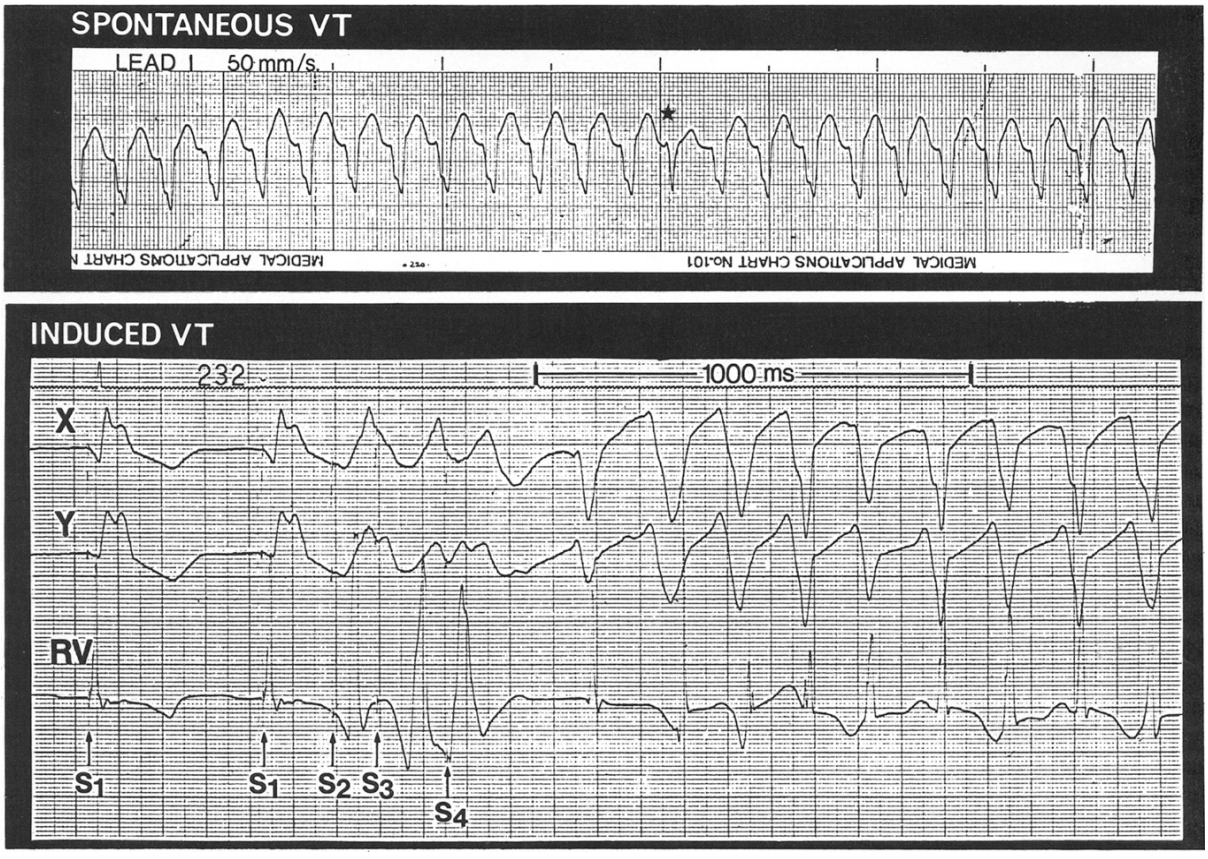

Figure 3. Dog 5 (Table 3). Tracings of spontaneous postinfarction ventricular tachycardia (VT) (**top tracing**) and ventricular tachycardia induced in the same dog by programmed stimulation (**bottom tracing**). Spontaneous ventricular tachycardia is documented electrocardiographically (lead I, 50 mm/s). Note the sinus fusion beat (*). Ventricular tachycardia of a similar configuration is induced by programmed stimulation with three extrastimuli (**bottom tracing**). Lead X is a surface Frank vectorcardiographic lead and is comparable with lead I in the top trace. RV = right ventricle; S = extrastimulus.

their center, but have irregular margins, particularly in the subepicardium at the infarct border. This model is, therefore, intermediate between those used by Garan et al. (7) and Duff et al. (8).

Previous human studies. These studies have provided conflicting evidence on the changes in the inducibility of ventricular tachycardia with infarct age. Patients who have experienced spontaneous ventricular tachycardia maintain a high rate of ventricular tachycardia induction for many months after infarction (16,17). However, when survivors of myocardial infarction who have not experienced spontaneous ventricular tachycardia are studied, reproducibility of induction between 2 weeks and 5 to 12 months is only 46% to 62% (3,4,18). Furthermore, delayed potentials recorded on the signal-averaged ECG, considered to be a marker of the arrhythmia substrate, disappear in the first 12 months after infarction in 33% to 50% of patients without spontaneous ventricular tachycardia (19,20).

Present study. The present study indicates that the decline in the reproducibility of ventricular tachycardia observed during human studies probably reflects changes occurring shortly after the initial electrophysiologic study, rather than in the months intervening between studies. Data from the current study indicate that the ideal time for prognostic study is 2 to 4 weeks after myocardial infarction. However, most patients are discharged from the hospital 7 to 10 days after uncomplicated infarction, and most late sudden deaths occur in the first few weeks after discharge (21). Presumably, patients remain at risk during the period that their arrhythmia remains inducible, even though that tendency may ultimately disappear. More detailed studies in human patients are required to evaluate the time course of loss of inducibility after infarction so that appropriate strategies may be developed to provide short- and long-term protection for the patient at risk. It should be noted that no dog developed inducible ventricular tachycardia in later weeks if the initial study showed no inducible arrhythmia.

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Inducible ventricular fibrillation may transform to inducible ventricular tachycardia in subsequent weeks, but the rate of crossover is low (2 of 7 cases [28%]).

High reproducibility of ventricular tachycardia inducible late after myocardial infarction. Although early ventricular tachycardia is labile, the present study also shows that ventricular tachycardia induced 2 weeks after infarction is highly reproducible for at least 4 months and probably longer. This finding confirms observations made over shorter periods of time by other investigators (7,22,23). Thus, this model of myocardial infarction using single stage left anterior descending coronary artery occlusion results in ventricular tachycardia that is suitable for testing the effects of a wide range of antiarrhythmia drugs, surgical procedures or electric devices.

Relation between induced and subsequent spontaneous arrhythmias. The late spontaneous ventricular tachycardia that occurred after infarction in the present study was rapid (cycle length 150 to 220 ms) and could be terminated by overdrive ventricular pacing or direct current shock in the majority of dogs. Therefore, it was different from the termination-resistant accelerated idioventricular rhythms observed by Garan et al. (7) 7 days after infarction. Electrophysiologic study conducted in seven dogs with spontaneous ventricular tachycardia yielded inducible ventricular tachycardia similar to that observed spontaneously in six dogs, a rate of induction similar to that observed in humans with spontaneous postinfarction ventricular tachycardia (24).

The tendency of dogs with inducible ventricular tachycardia to be at risk for spontaneous ventricular tachycardia is also remarkably similar to that reported in human studies. Denniss et al. (3) showed that 21% of patients with inducible ventricular tachycardia of cycle length >230 ms ("slow ventricular tachycardia") after acute myocardial infarction developed late (within 1 year) spontaneous ventricular tachycardia or sudden death. Canine ventricular tachycardia is more rapid than human postinfarction ventricular tachycardia. In our experience, canine ventricular tachycardia with a cycle length of 140 ms is usually well tolerated and this is, therefore, a suitable cutoff point for canine "slow ventricular tachycardia." In the present study, 22% of animals with inducible ventricular tachycardia of cycle length >140 ms developed late spontaneous ventricular tachycardia or sudden death. Because continuous ECG monitoring was not used late after infarction, this percent should be regarded as an underestimate. However, the similarity between human and canine studies illustrates the value and applicability of this canine model.

Canine model of late postinfarction ventricular tachycardia. The failure of other laboratories to produce a model with high ventricular tachycardia inducibility and reproducibility may have several causes. First, there is considerable potential in the canine heart for establishment of collateral circulation, and the proportion of ventricle infarcted has been shown to influence the rate of induction of ventricular tachycardia (8). It is necessary to ligate at least one diagonal branch in addition to the left anterior descending coronary artery to ensure a high yield of inducible ventricular tachycardia. Second, from the results of the present study, it can be seen that ventricular tachycardia must be inducible at least 2 weeks after infarction to ensure subsequent high reproducibility. Finally, the protocol for programmed stimulation must be aggressive enough to overcome the influence of day to day variability in extrastimulus requirements. In the present study, an average of three to four extrastimuli were required for induction of ventricular tachycardia. We recommend the use of at least five extrastimuli to ensure reproducibility of tachycardia induction from study to study. In our experience, 97% of dogs require five or fewer extrastimuli for tachycardia induction. The use of more than five extrastimuli only serves to increase the incidence of unwanted ventricular fibrillation.

Possible limitations. *Influence of anesthesia.* General anesthesia was employed in 45% of studies in the present investigation. These studies were all performed within the first 4 weeks after infarction. The anesthetic regimens used were either standard for canine experimental anesthesia or have been shown by our laboratory (9) not to influence the outcome of programmed stimulation. The same agent was always used in each individual dog, thereby eliminating study to study variability due to effects of anesthesia. Furthermore, results from the 21 dogs studied without anesthesia during the same interval did not differ significantly in terms of electrophysiologic variables or arrhythmia inducibility.

Animals with no inducible arrhythmia. Although our study showed ventricular tachycardia to be highly reproducible, it did not adequately address the issue of whether inducibility may develop in the weeks after myocardial infarction. Only a small number of dogs with no inducible arrhythmia were studied, and these were studied only on two occasions each. Further investigation is warranted to clarify this important issue.

Conclusions. Significant changes in the induction of ventricular tachycardia occur during the healing phase of myocardial infarction (1 to 4 weeks). If a stable long-term animal model of ventricular tachycardia is required, programmed stimulation should be conducted beyond this time. The reproducibility of ventricular tachycardia induction >4 weeks after infarction is very high, making this model suitable for investigation of a wide range of antiarrhythmic interventions.

Spontaneous ventricular tachyarrhythmias occur in approximately 20% of dogs with inducible "slow" ventricular tachycardia in the 1st 2 months after infarction. This is similar to the rate of development of spontaneous ventricular tachycardia in asymptomatic human patients with inducible ventricular tachycardia 2 weeks after infarction. This canine

model of postinfarction ventricular tachycardia, therefore, has many important similarities to the human arrhythmia.

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